MAKING THE USE OF ALTERNATIVE METHODS A REALITY

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Introduction

- Increasing numbers of alternatives to animal testing are being developed, validated, and accepted by regulatory agencies
- However, use of these methods by industry in some cases remains low (example - eye irritation alternatives for antimicrobial cleaning products [AMCPs])
- What are the challenges and barriers to use?
- What actions can lead to greater uptake?

Safety Evaluation of Cleaning Products

- In the U.S., the safety of most household cleaning products can be assessed by the manufacturer without the use of animals
- Products with antimicrobial claims are treated as pesticides and regulated by EPA
- In addition to five other acute toxicity tests, EPA requires that eye irritation potential be determined

Photo by R. Curren

U.S. EPA Office of Pesticide Programs Classification and Labeling System

Toxicity Category	Signal Words	Eye Hazard Statements
I	DANGER	Corrosive (causes irreversible eye damage). Wear appropriate protective eyewear such as goggles, face shield, or safety glasses.
II	WARNING	Causes substantial but temporary eye injury. Wear appropriate protective eyewear such as goggles, face shield, or safety glasses.
III	CAUTION	Causes moderate eye irritation. May wear protective eyewear, if appropriate (not required).
IV	CAUTION (optional)	No statements are required. However, the registrant may choose to use category III labeling.

Tests Used

- Historically, Draize test in rabbits used to classify AMCPs
- Collaboration between industry and regulators led to development of an alternative approach using *in vitro* and *ex vivo* assays in place of animal tests

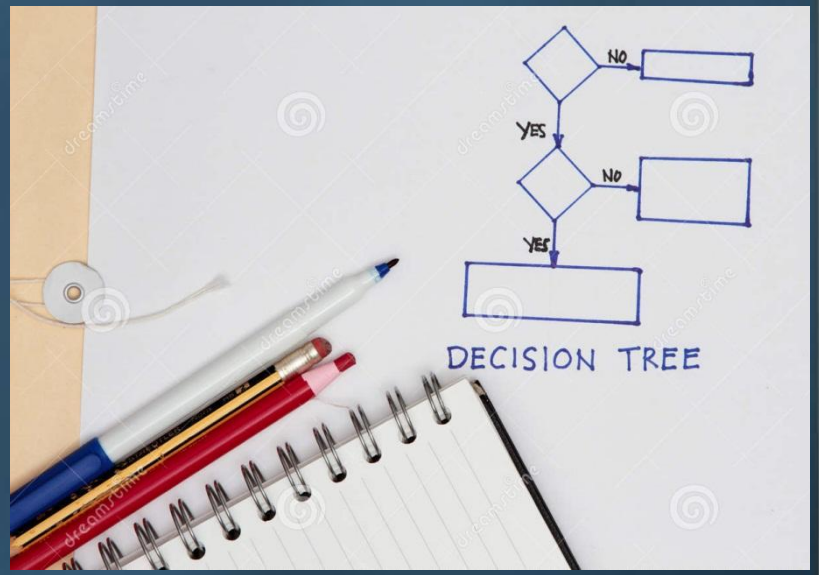
Steps Taken

- Collaboration in 2004 between EPA, seven AMCP manufacturers, the Institute for In Vitro Sciences (IIVS), and the Accord Group
- Companies provided existing data for the same product derived from both animal and alternative tests, which allowed for a retrospective comparative analysis
- Additional *in vitro* testing performed to verify final prediction model

Steps Taken

- An 18-month pilot program was initiated in 2009 during which companies were encouraged to submit eye irritation studies using the alternative methods

- Analysis of data and development of a **decision tree framework** utilizing three alternative eye irritation assays



The Assays*

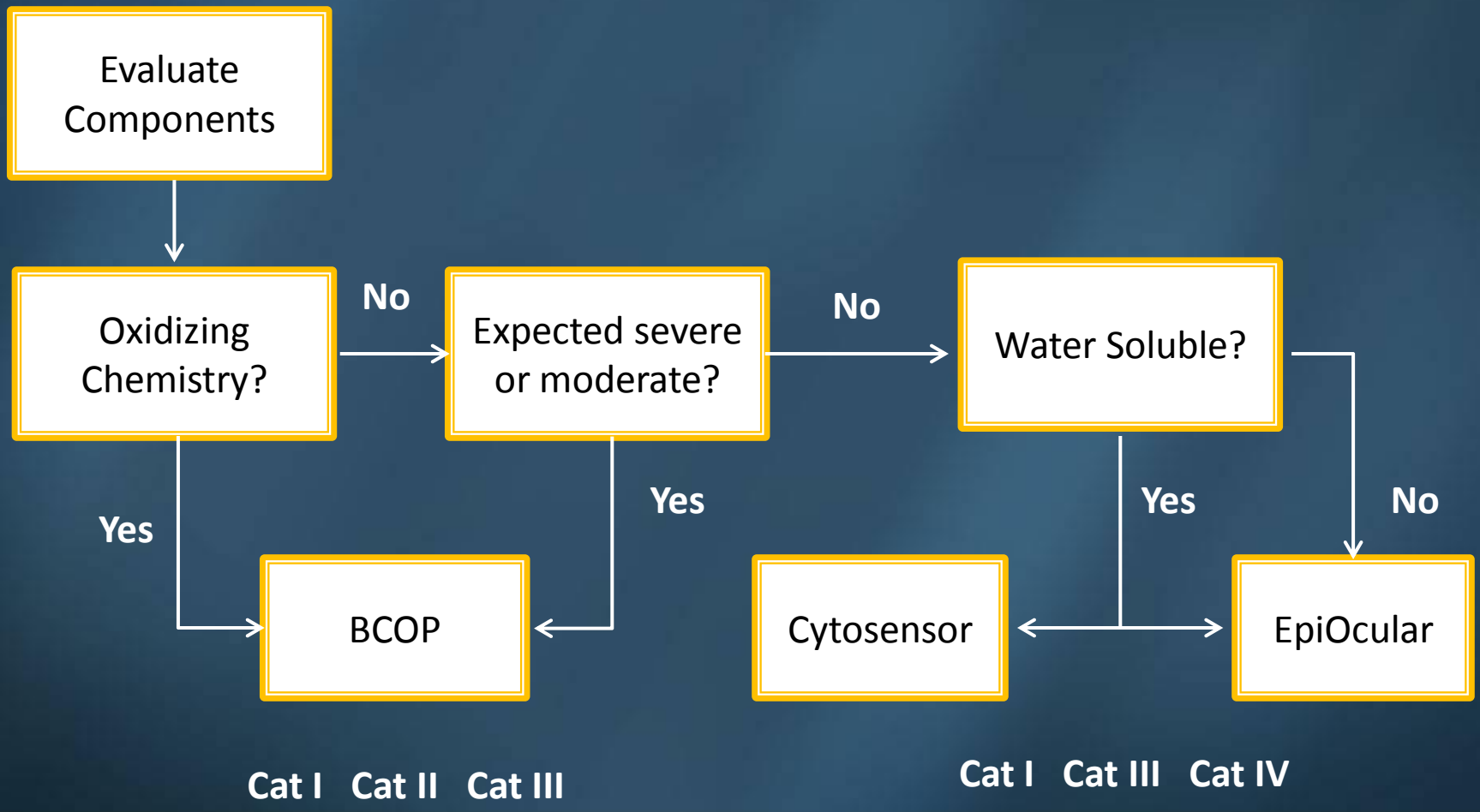
Bovine Corneal Opacity and Permeability assay
OECD Test Guideline 437
EPA categories I, II, or III

Cytosensor™ Microphysiometer
OECD draft Test Guideline
EPA categories I, III, or IV

EpiOcular™ assay (MatTek Corp.)
OECD Test Guideline 492
EPA categories I, III, or IV

*Assay protocols may deviate slightly from OECD TGs

Decision tree: Selection and evaluation of assays for EPA eye hazard labeling



Outcomes

- Effort was successful in demonstrating collaboration between the EPA and stakeholders
- Effort was successful in demonstrating that AMCPs could be classified into one of the EPA's four eye hazard categories without the use of live animals
- In May 2013, the EPA issued a policy document that allowed for use of alternatives to predict eye irritation potential of AMCPs and, on a case-by-case basis, of conventional pesticides

Follow-up

- EPA reports that only 10 AMCPs (<10%) have been registered using the alternative approach (includes those from 2009 pilot program)
- Reasons for the lack of use?
  - A questionnaire was sent by IIVS to major AMCP manufacturers in the spring of 2015 asking them if they were still using the animal test and, if so, why?
  - Results were provided anonymously

Results of Questionnaire

- Lack of global regulatory acceptance (likely will have to do the animal test anyway)
- Uncertainty over reviewer familiarity with new approach and acceptance of data; time and cost if it takes longer to register product as a result
- Concern about overestimation of hazard category
- Time and cost for doing both animal test and non-animal test(s)

Actions that can be taken to address barriers to use of alternative methods

Global Regulatory Acceptance

- Critical to uptake of new methods, particularly for products marketed worldwide
- For companies to move away from animal testing and invest in new methods, has to make sense economically (i.e., not have to do 2 tests)
- Companies in forefront can encourage those countries lagging behind; highlight non-animal testing as important international trade issue
- U.S. EPA can foster global harmonization through various international forums (e.g., ICATM)

Reviewer Awareness & Training

- Reviewer unfamiliarity may lead to rejection of the application, a slower approval time, and fewer submissions by other companies that want to avoid delays
- Regulatory agency has to ensure its reviewers are aware of and trained in the new methods
- Training should be in a variety of forms and take place across all sectors and levels of management within the organization

Incentives for Using Alternative Methods

- Regulatory agency should proactively prepare for incoming registration submissions to avoid delays so that a company's first experience goes smoothly
- Agency consider providing expedited review of those using alternatives to encourage more use
- Companies should be persistent if they think alternative submissions are being delayed or have gotten rejected in error

Accurate Prediction of Hazard

- Possibility of over-prediction of the hazard class by the alternative approach when compared to the animal test, which raises concern with company
- Industry & regulators reach agreement regarding acceptable level of over- and under-prediction compared to animal test and modify prediction algorithm of alternatives, if needed
- Modify subjective category ranges derived from animal test without adversely affecting safety, if appropriate

Continued Collaboration

- Regulators and industry need to overcome institutional inertia and continue to work together, provide leadership, take risks
- Industry must be willing to face rough patches (e.g., potentially delayed registration) and persevere
- Regulators must continue to commit resources to training and incentives even in the face of initial low industry participation

Ongoing Interaction and Outreach

- Continuing dialog between industry and regulators to discuss obstacles and experiences
- Regulators and NGOs can provide outreach to smaller companies to alert them to the new policies
- NGOs can help organize collaborative training sessions for regulators and industry
- Monitor success of program and provide feedback

Transition from Voluntary to Mandatory

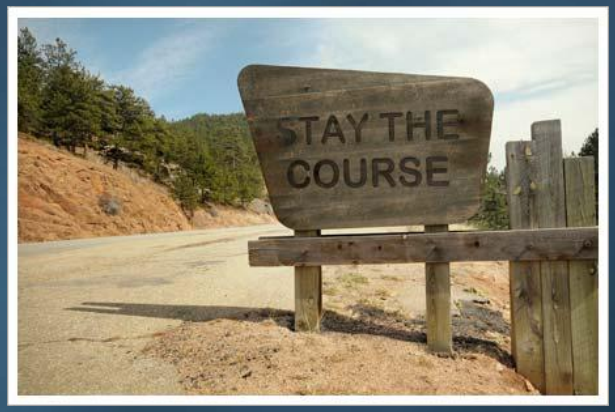
- Currently EPA considers non-animal eye irritation methods as *alternatives*, not replacements
- Use by industry is voluntary
- At some point, if validated alternatives to animal testing are available, shouldn't use become mandatory?
- EU, India, Israel and Norway legislative bans on cosmetics testing on animals
- EU REACH program: animal testing as a last resort

Conclusions

- Implementation of new test methods is a multi-step process that does not end with enactment of a policy
- To achieve widespread use, it requires:
  - Planning, data collection/analysis, validation
  - Policy development, public comment, outreach
  - Education of regulators and industry personnel
  - Continued dialog among stakeholders, monitoring, and feedback
  - Global acceptance
  - Transition from voluntary to mandatory

Conclusions (cont.)

- The same strategies recommended for enhancing use of the eye irritation alternative framework can be applied when facilitating the uptake of other non-animal approaches in the future
- Successful implementation will depend on both industry and regulators staying the course and providing leadership in carrying out the new 21st Century toxicity testing paradigm



EPA Progress

- Recent announcements regarding acute testing @ https://www.epa.gov/pesticides/new-epa-guidance-testing-pesticides-will-reduce-animal-testing
  - Open letter to stakeholders from OPP Director describing progress in reducing the use of animals in acute toxicity tests
  - Final guidance issued: “Process for establishing and implementing alternative approaches to traditional *in vivo* acute toxicity studies”
  - Draft policy to waive acute dermal toxicity tests performed on animals for pesticide formulation registrations based on acute oral data

EPA Progress (cont.)

- Evaluating paired *in vivo*/*in vitro* eye irritation data for conventional pesticides
- Investigating the use of *in vitro* skin sensitization assays to replace animal tests; seeking paired *in vivo*/*in vitro* data for use with pesticides
- Exploring ways to transition from EPA's current classification system to the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) Hazard Categories for product labeling

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Eye Irritation Project

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